General

Guideline Title

BSR and BHPR guidelines on the use of rituximab in rheumatoid arthritis.

Bibliographic Source(s)

Bukhari M, Abernethy R, Deighton C, Ding T, Hyrich K, Lunt M, Luqmani R, Kiely P, Bosworth A, Ledingham J, Ostor A, Gadsby K, McKenna F, Finney D, Dixey J, BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guidelines on the use of rituximab in rheumatoid arthritis. London (England): British Society for Rheumatology; 2011. 9 p. [52 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The levels of evidence (I-IV) supporting the recommendations and ratings of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Can Rituximab Be Given without Other Disease Modifying Antirheumatic Drugs (DMARDs), or with Alternatives to Methotrexate (MTX)?

Recommendation 1: If MTX is contra-indicated, rituximab should be used in rheumatoid arthritis (RA) either alone, or with leflunomide (LEF). (Level III evidence, Grade of recommendation B)

Can Rituximab Be Given before Anti-Tumour Necrosis Factor (anti-TNF) Therapy, and Are There Any Particular Categories of RA Patients Who Might Benefit from Such an Approach?

Recommendation 2: Rituximab could be given in RA before anti-TNF treatment, particularly in patients who have an absolute or relative contra-indication to anti-TNF therapy. (Level Ib evidence, Grade of recommendation A)

Should the Eligibility and Response Criteria Be Modified?

Recommendation 3: Rituximab should be given in patients with active RA who have failed one or more biologics, or who are intolerant, or have contra-indication, to anti-TNF therapy. It should be borne in mind that patients who are rheumatoid factor (RF) positive or anti-citrullinated protein antibody (ACPA) positive are more likely to respond to rituximab than patients who are negative for both these antibodies. (Level Ia evidence, Grade of recommendation A)

Recommendation 4: RA patients on rituximab should be assessed for response at an interval of no less than 16 weeks and ideally at 24 weeks.

Patients who do not show at least a moderate European League Against Rheumatism (EULAR) response to the first treatment course should not be considered for re-treatment. (Level Ia evidence, Grade of recommendation A)

Should the Suggested Frequency of Repeat Infusions be Modified?

Recommendation 5: Re-treatment with rituximab in RA should be considered when initial treatment response of at least a moderate EULAR response has been lost. The frequency of infusion should be no less than 24 weeks. (Level III evidence, Grade of recommendation B)

Safety Aspects

Recommendation 6: Etanercept should be stopped 4 weeks before and adalimumab and infliximab 8 weeks before commencing rituximab therapy in RA. (Level IV evidence, Grade of recommendation C)

Recommendation 7: Commencement of biologic therapy following treatment with rituximab should only be done with caution. (Level IV evidence, Grade of recommendation C)

Recommendation 8: Immunoglobulin levels should be checked before commencing rituximab in RA, as well as 4-6 months after infusions and before any re-treatment. It is recommended that the possibility of increased risk of infection in patients with low immunoglobulin G (IgG) <6 g/l be discussed with patient before re-treatment with rituximab. (Level IV evidence, Grade of recommendation C)

Recommendation 9: Repeat treatment with rituximab in RA should be decided on clinical grounds, not on B-cell numbers. (Level III evidence, Grade of recommendation B)

Recommendation 10: Rituximab is contra-indicated in RA patients with active infection or severely immunocompromised patients (e.g., in hypogammaglobulinaemia or where levels of CD4 or CD8 are very low). Caution should be exercised when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infection. (Level IV evidence, Grade of recommendation C)

Recommendation 11: Patients who have not already had pneumococcus immunization should ideally receive this 4-6 weeks before commencing first course of rituximab. (Level IIa evidence, Grade of recommendation B)

Recommendation 12: Patients should receive influenza vaccination before rituximab treatment and annually (before rituximab re-treatment if possible) at a time when B cells are likely to be returning. (Level IIa evidence, Grade of recommendation B)

Recommendation 13: Screening of risk factors for hepatitis B and C infection should be undertaken in all patients before going on to rituximab. In patients who are hepatitis B virus (HBV) positive, a risk:benefit assessment should be undertaken, as treatment may be safe if appropriate anti-viral treatment is given. Rituximab treatment may be safe in patients with hepatitis C, but there are reports of severe infusion reactions in up to 25% of these patients. Hepatitis serology should be monitored in patients with evidence of past or present current hepatitis B or C infection. (Level IV evidence, Grade of recommendation C)

Recommendation 14: No re-treatment with rituximab and prompt reduction or discontinuation of other immunosuppressants should be undertaken when progressive multifocal leucoencephalopathy (PML) is suspected, and appropriate investigations should be undertaken. (Level IV evidence, Grade of recommendation C)

Definitions:

Levels of Evidence

Level	Evidence
Ia	Meta-analysis of randomised controlled trials (RCTs)
Ib	At least one RCT
IIa	At least one well-designed controlled study, but without randomisation
IIb	At least one well-designed quasi-experimental design
III	At least one non-experimental descriptive study (e.g., comparative, correlation, or case study)
IV	Expert committee reports, opinions, and/or experience of respected authorities

Grades of Recommendations

Grade	Type of Evidence
A	Meta-analysis of randomised controlled trials (RCTs) *or* at least one RCT
B	Well-designed controlled study but without randomisation *or* well-designed quasi-experimental study *or* well-designed descriptive study
C	Expert committee reports, opinions, *and/or* experience of respected authorities

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Rheumatoid arthritis

Note: This guideline does not cover other rheumatological conditions.

Guideline Category

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide guidelines to assist the rational prescribing of rituximab by updating the information provided in National Institute for Health and Clinical Excellence (NICE) guidance and the European League Against Rheumatism (EULAR) consensus statement on use of rituximab in patients with rheumatoid arthritis (RA) published in January 2007

Target Population

Patients with rheumatoid arthritis

Interventions and Practices Considered

1. Rituximab alone or with leflunomide
2. Timing of rituximab administration in relation to anti-tumor necrosis factor (TNF), etanercept, adalimumab, and immunizations
3. Assessing eligibility for and response to rituximab therapy
4. Frequency of re-treatment
5. Screening for immunoglobulin G levels and risk factors for hepatitis B or C infection
6. Management if progressive multifocal leucoencephalopathy (PML) is suspected

Major Outcomes Considered

- Treatment response rates, e.g., measured by American College of Rheumatology (ACR) criteria
- Duration of treatment response
- Reduction or inhibition of joint damage
- Burden of inflammation
- Number of flares
- Treatment side effects
- Immunization response rates

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The current National Institute for Health and Clinical Excellence (NICE) eligibility and response criteria were reviewed, and evidence was sought to determine whether these should be modified and also whether there was evidence available to update the European League Against Rheumatism consensus statement particularly regarding safety issues. This evidence was sought through a MEDLINE search using keywords rituximab and RA to identify English language articles published before April 2010 and also a manual search of databases from the British Society for Rheumatology (BSR) and EULAR annual meetings in 2007-2010. The American College of Rheumatology (ACR) meetings from 2007-2009 were also searched.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

Level	Evidence
Ia	Meta-analysis of randomised controlled trials (RCTs)
Ib	At least one RCT
IIa	At least one well-designed controlled study, but without randomisation
IIb	At least one well-designed quasi-experimental design
III	At least one non-experimental descriptive study (e.g., comparative, correlation, or case study)
IV	Expert committee reports, opinions, and/or experience of respected authorities

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Evidence was graded according to the strength of literature to support each statement, using the grading suggested by the Royal College of Physicians of London.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The document was prepared in accordance with the principles outlined in the Appraisal of Guidelines Research and Evaluation (AGREE) guidelines .

The current National Institute for Health and Clinical Excellence (NICE) eligibility and response criteria were reviewed, and evidence was sought to determine whether these should be modified. An update on safety aspects based on the increasing experience of this drug was performed to advise colleagues regarding toxicity and the safe use of the drug.

Eligibility and Response Criteria

Current NICE guidelines state that rituximab should be:

i. Used with methotrexate (MTX)
ii. Used in patients who have had an inadequate response to or intolerance of other disease-modifying antirheumatic drugs (DMARDs), including treatment with at least one anti-tumour necrosis factor (TNF) therapy
iii. Used by specialist physicians experienced in diagnosis and treatment of rheumatoid arthritis (RA)
iv. Continued only if patients show an improvement in disease activity of ≥1.2 points
v. Given with MTX in repeated courses and for not >6 months

The group discussed this and raised several questions after scrutinizing the current evidence:

i. Can rituximab be given without other DMARDs, or with alternatives to MTX?
ii. Can rituximab be given before anti-TNF therapy, and are there any particular categories of RA patients who might benefit from such an approach?
iii. Should the eligibility and response criteria be modified?
iv. Should the suggested frequency of repeat infusions be modified?

v. Should the safety of the drug be reviewed?

Rating Scheme for the Strength of the Recommendations

Grades of Recommendations

Grade	Type of Evidence
A	Meta-analysis of randomised controlled trials (RCTs) *or* at least one RCT
B	Well-designed controlled study but without randomisation *or* well-designed quasi-experimental study *or* well-designed descriptive study
C	Expert committee reports, opinions, *and/or* experience of respected authorities

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The guidelines have been reviewed by members of the National Rheumatoid Arthritis Society.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of rituximab in rheumatoid arthritis

Potential Harms

- Side effects of treatment, including serious infection events, low immunoglobulin G (IgG) levels, re-activation of hepatitis B, decreased response to immunization, and severe infusion reactions
- Caution should be exercised when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infection.

Contraindications

Contraindications

Rituximab is contra-indicated in rheumatoid arthritis (RA) patients with active infection or severely immunocompromised patients (e.g., in hypogammaglobulinaemia or where levels of CD4 or CD8 are very low).

Implementation of the Guideline

Description of Implementation Strategy

How Will These Guidelines Be Publicized and Implemented?

The full guidelines will be published on the British Society for Rheumatology (BSR) Web site, and sent to all BSR members and primary care trusts. A summary of the guidelines will be published in Rheumatology, with web links to the full guidelines. Implementation of some parts will depend on negotiations with the National Institute for Health and Clinical Excellence (NICE), whereas aspects of safety can be implemented on publication.

Implementation Tools

Audit Criteria/Indicators

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011

Guideline Developer(s)

British Health Professionals in Rheumatology - Professional Association

British Society for Rheumatology - Medical Specialty Society

Source(s) of Funding

No funding has been received to assist with the development of these guidelines.

Guideline Committee

BSR and BHPR Standards, Guidelines and Audit Working Group

Composition of Group That Authored the Guideline

Working Group Members: Marwan Bukhari, Rheumatology Department, University Hospitals of Morecambe Bay NHS Foundation Trust, Royal Lancaster Infirmary, Lancaster; Rikki Abernethy, Rheumatology Department, St Helens Hospital, St Helens; Chris Deighton, Rheumatology Department, Derbyshire Royal Infirmary, Derby; Tina Ding, Rheumatology Department, Derbyshire Royal Infirmary, Derby; Kimme Hyrich, Arthritis Research UK Unit, University of Manchester, Manchester; Mark Lunt, Arthritis Research UK Unit, University of Manchester, Manchester; Raashid Luqmani, Rheumatology Department, Nuffield Orthopaedic Centre, Oxford; Patrick Kiely, Rheumatology Department, St George's Healthcare, London; Ailsa Bosworth, National Rheumatoid Arthritis Society, Maidenhead; Jo Ledingham, Rheumatology Unit, Queen Alexandra Hospital, Portsmouth; Andrew Ostor, Rheumatology Department, Addenbrooke's Hospital, Cambridge; Kate Gadsby, Rheumatology Department, University Hospitals of Morecambe Bay NHS Foundation Trust, Royal Lancaster Infirmary, Lancaster; Frank McKenna, Rheumatology Department, Trafford General Hospital, Manchester; Diana Finney, Rheumatology Unit, Worthing and Southlands NHS Trust; Josh Dixey, Rheumatology Department, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, UK

Financial Disclosures/Conflicts of Interest

M.B. has attended meetings organized by Schering-Plough, has been sponsored to attend international meetings by Pfizer, Merck, Roche, Wyeth and Abbott, and has accepted honoraria for educational meetings from Merck, Wyeth, Abbott, Roche, Union Chimique Belge (UCB) celltech, Mennarini, and Pfizer. He has also departmental sponsorship for software from Wyeth, Abbott, and Roche. P.K. has received departmental support for research and education, and/or honoraria for advisory board work from Abbott, MSD, Napp, Pfizer, Roche, and UCB. F.M. has received honoraria from Roche for participation in advisory boards and has participated in clinical trials with Roche compounds. R.L. has received financial support from Roche, Pfizer, and Wyeth to attend scientific conferences (American College of Rheumatology [ACR] and European League Against Rheumatology [EULAR]); honoraria from UCB to give talks; and has provided consultancy advice to MSD. R.A. holds departmental sponsorship from Roche, Wyeth, Abbott, and Schering-Plough for academic meetings. She has received personal sponsorship from Wyeth, Abbott, and UCB to attend international educational meetings, is involved with commercial trial recruitment in rheumatoid arthritis (RA) from Roche and has previously sat on an advisory board for Roche. A.O. has received support from (including attendance at conferences), undertakes clinical trials and acts as a consultant to Roche, Chugai, Schering-Plough/MSD, Abbott, Wyeth, Bristol-Myers Squibb, GSK, MerckSorono, and UCB. C.D. works for the Royal Derby hospital that has received a grant from Roche to fund a research nurse and has been involved in clinical trials of Roche drugs. A.B.'s organization, the National Rheumatoid Arthritis Society, has received educational grants for projects undertaken by the charity in 2010. All other authors have declared no conflicts of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Rheumatology Journal Web site .

Availability of Companion Documents

The following is available:

- Bukhari M, Abernethy R, Deighton C, Ding T, Hyrich K, Lunt M, Luqmani R, Kiely P, Bosworth A, Ledingham J, Ostör A, Gadsby K, McKenna F, Finney D, Dixey J; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guidelines on the use of rituximab in rheumatoid arthritis. Executive summary. Rheumatology (Oxford). 2011 Dec;50(12):2311-3. Electronic copies: Available on Portable Document Format (PDF) from the Rheumatology Journal Web site .

In addition, an audit tool is available from the British Society for Rheumatology Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 31, 2012. The information was verified by the guideline developer on February 13, 2013. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab).

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